REMARKS

This amendment responds to the office action mailed November 20, 2002. In the office action the Examiner:

1-2. objected to the drawings as containing incorrect reference numerals;

3. objected to the specification because of a number of informalities;

4-6. rejected claim 7 under 35 U.S.C. 112 as being indefinite;

7-8. rejected claims 1, 11-16, 19, and 20 under 35 U.S.C. 102(b) as being anticipated by Tatsumi *et al.* (U.S. Patent No. 4,634,490) (hereinafter "Tatsumi");

9. rejected claims 1, 2, 3, 11-16, 19, and 20 under 35 U.S.C. 102(b) as being anticipated by Murayama. (U.S. Patent No. 5,046,077) (hereinafter "Murayama");

10-11. rejected claim 4 under 35 U.S.C. 103(a) as being unpatentable over Tatsumi in view of Fink *et al.* (U.S. Patent No. 5,359,640) (hereinafter "Murayama");

12. rejected claims 5-7 under 35 U.S.C. 103(a) as being unpatentable over Tatsumi in view of Stettner *et al.* (U.S. Patent No. 5,629,524) (hereinafter "Stettner");

13. rejected claim 8 under 35 U.S.C. 103(a) as being unpatentable over Tatsumi in view of Cullity;

14. rejected claim 9 under 35 U.S.C. 103(a) as being unpatentable over Tatsumi in view of Dosho (U.S. Patent No. 6,285,736) (hereinafter "Dosho");

15. rejected claim 10 under 35 U.S.C. 103(a) as being unpatentable over Tatsumi in view of Polichar *et al.* (U.S. Patent No. 6,205,199) (hereinafter "Polichar");

16. rejected claims 17 and 18 under 35 U.S.C. 103(a) as being unpatentable over Tatsumi as applied to claim 16 above;

17. rejected claim 21 under 35 U.S.C. 103(a) as being unpatentable over Tatsumi as applied to claim 20 above;

18. rejected claim 22 under 35 U.S.C. 103(a) as being unpatentable over Tatsumi in view of Arnowitz *et al.* (U.S. Patent No. 6,468,346) (hereinafter "Arnowitz").

19. rejected claims 23 and 24 under 35 U.S.C. 103(a) as being unpatentable over Tatsumi as applied to claim 11 above;

20. rejected claim 4 under 35 U.S.C. 103(a) as being unpatentable over Murayama in view of Fink;

21. rejected claims 5-7 under 35 U.S.C. 103(a) as being unpatentable over Murayama in view of Stettner;

22. rejected claim8 under 35 U.S.C. 103(a) as being unpatentable over Murayama in view of Cullity;

23. rejected claim 9 under 35 U.S.C. 103(a) as being unpatentable over Murayama in view of Dosho;

24. rejected claim 10 under 35 U.S.C. 103(a) as being unpatentable over Murayama in view of Polichar;

25. rejected claims 17 and 18 under 35 U.S.C. 103(a) as being unpatentable over Murayama as applied to claim 16;

26. rejected claim 21 under 35 U.S.C. 103(a) as being unpatentable over Murayama as applied to claim 20;

27. rejected claim 22 under 35 U.S.C. 103(a) as being unpatentable over Murayama in view of Arnowitz;

28. rejected claims 23 and 24 under 35 U.S.C. 103(a) as being unpatentable over Murayama as applied to claim 11;

29. rejected claims 25-27 under 35 U.S.C. 103(a) as being unpatentable over Murayama;

30. rejected claim 28 under 35 U.S.C. 103(a) as being unpatentable over Murayama in view of Fink;

31. rejected claim 29 under 35 U.S.C. 103(a) as being unpatentable over Murayama as applied to claim 25 and further in view of Arnowitz; and

32. rejected claims 30 and 31 under 35 U.S.C. 103(a) as being unpatentable over Murayama as applied to claim 25.

Applicant will address each of the Examiners objections and rejections sequentially. The paragraph numbers correspond to those of the Examiner's for ease of reference.

Furthermore, a number of amendments have been made to the claims to further clarify the invention. These amendments are not in response to any rejection by the Examiner, i.e., not for purposes of patentability. For example, the term "suitable" has been added to claims 1, 11, and 25. Support for this amendment can be found at page 5, lines 17-22. Also, claims

1 and 11 have been amended to further clarify that the method requires determining whether a crystal exists before it is irradiated. Support for these amendments can be found at page 3, lines 17 and 18; and page 7, lines 3 and 4.

Still further, new claims 32 to 38 have been added. Support for these new claims can be found on page 5 and 11, claim 2, and the figures.

Drawings

1. The Examiner has objected to the drawings as failing to comply with 37 CFR 1.84(p)(4) because reference character "126" has been used to designate both an upstanding column and a beam stop. Figure 1 and the specification have been amended to alter the reference numeral for the beam stop from 126 to 127.

2. The Examiner has objected to the drawings as failing to comply with 37 CFR 1.84(p)(5) because they include the following reference sign(s) not mentioned in the description: 508 in Fig. 5. Figure 5 has been amended to remove any reference to numeral 508.

Specification

3. The Examiner has objected to the disclosure because of the following informalities:

(1) Page 9, line 15, "128" should be replaced by --132--. The paragraph in question has been amended to address this objection.

(2) Page 14, line 16, a space should be inserted after "4". The paragraph in question has been amended to address this objection.

Claim Rejections - 35 USC § 112

4-6. The Examiner has rejected claim 7 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular the Examiner states that

> [t]he terms "high sensitivity" and "rapid readout" in claim 7 are relative terms which renders the claim indefinite. The terms "high sensitivity" and "rapid readout" are not defined by the claim, the specification does not provide

> a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.
> The specification fails to qualify these two terms. (Emphasis added)

Applicant cancels claim 7, with traverse, as the plain meaning of the terms "high sensitivity" and "rapid readout" are indeed defined in the specification. For example, an X-ray detector having a "high sensitivity" has a sensitivity similar to that provided by phosphor plates[1]. Similarly, an X-ray detector having a "rapid readout" has a speed of readout similar to that provided by a CCD camera[2]. Accordingly, these terms are not indefinite, as the specification qualifies these terms.

Claim Rejections - 35 USC § 102

7-8. The Examiner has rejected claims 1, 11-16, 19, and 20 under 35 U.S.C. 102(b) as being anticipated by Tatsumi. Applicants respectfully traverse this rejection.

For a prior art reference to anticipate a claim, each and every element of the claim must be identically shown in a single reference.[3]

Tatsumi relates to methods of controlling crystal growth for use in semiconductors or optical devices,[4] and more specifically to a "method of monitoring a single crystal during growth...during growth of the crystal produced by a pulling up method or a floating melting accumulation method."[5] Thus, Tatsumi presupposes the existence of crystalline material. Quite unlike Tatsumi, the present invention initially determines whether any suitable crystalline material is present at all, before irradiating the located crystalline material. Instead, Tatsumi does not initially identify the presence of crystalline material, but rather presupposes its existence. Accordingly, Tatsumi cannot anticipate the claims of the present invention.

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[1]*See* page 11, lines 17-19.

[2]*Id.*

[3]*See In re Bond,* 910 F.2d 831 (Fed. Cir. 1990).

[4]Tatsumi, col.1, ll.14-16.

[5]Tatsumi, col. 1, ll. 6-11.

Further evidence is provided in Tatsumi, which states that another "object of the present invention is to provide a method of monitoring the crystal growth which enables to visually recognize the crystal state instantly."[6] Consequently, Tatsumi teaches monitoring the growth of a crystal, rather than detecting the presence of crystalline material. Therefore, Tatsumi does not disclose or teach detecting the presence of crystalline material, as required by independent claims 1 and 11.

In light of the above, it is respectfully requested that this rejection be withdrawn, and that independent claims 1 and 11, and their dependent claims, be allowed.

9. The Examiner has rejected claims 1, 2, 3, 11-16, 19, and 20 under 35 U.S.C. 102(b) as being anticipated by Murayama (U.S. Patent No. 5,046,077). Applicants respectfully traverse this rejection.

Murayama relates to "a method...for measuring lattice spacings in particular of a single crystal during the growth thereof by vapor deposition while located in a heating furnace."[7] Just like Tatsumi, Murayama presupposes the existence of crystalline material. For example, Murayama states that the patent relates to "measuring the lattice constant ratio of a crystal."[8] In contrast to Murayama's focus on measuring lattice constant ratios of existing crystals, the present invention relates to detecting whether crystalline material is present at all, and, thereafter determining whether the crystalline material detected has the appropriate diffraction characteristics. Although, in the present invention, the crystal lattice may be analyzed to differentiate between a protein crystal and a non-protein crystal,[9] this is quite unlike Murayama's goal of measuring the lattice spacing during the growth of an existing crystal, to measure crystal quality.[10] Accordingly, Murayama does not disclose, teach, or suggest detecting the presence of a suitable crystalline material, as required by independent

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[6]Tatsumi, col. 2, ll. 5-7.

[7]Murayama, abstract.

[8]Murayama, col. 1, ll. 8-11.

[9]*See* page 4, ll. 13-16.

[10]*See* col. 1, ll. 14-16; col. 2, ll. 9-11.

claims 1 and 11.

In light of the above, it is respectfully requested that this rejection be withdrawn, and that independent claims 1 and 11, and their dependent claims, be allowed.

Claim Rejections - 35 USC § 103

10-11. The Examiner has rejected claim 4 under 35 U.S.C. 103, as unpatentable over Tatsumi, as applied to claim 1, and further in view of Fink . The Examiner states that:

> Tatsumi et al. disclosed an apparatus and method for detecting the presence of crystalline material in its in situ growth environment comprising a crystal growth incubator. However, Tatsumi et al. did not teach that the apparatus further comprising an imaging system disposed adjacent to the crystal incubator . . .

The Examiner then cites Fink et al. as disclosing a micro-diffractometer for aligning the X-ray with a micro-sized sample. Applicants respectfully traverse this rejection.

To establish a *prima facie* case of obviousness, three basic criteria must be met, namely:

1) There must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings;

2) There must be a reasonable expectation of success; and

3) The prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure.[11]

As stated above, Tatsumi does not teach the methods of the present invention, as Tatsumi does not teach <u>detecting the presence of crystalline material</u> as a method of improved screening of crystals and microcrystalline material with appropriate X-ray diffraction characteristics. In addition, Fink does not disclose, teach, or suggest initially <u>detecting the presence of crystalline material</u> before screening for suitability. Accordingly, the combination of Tatsumi and Fink does not teach or suggest all the claim limitations of Independent claim 1, from which claim 4 depends.

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[11] *See In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Claim 4 relates to the addition of an imaging system as part of the crystalline detection apparatus to detect the presence and location of crystals grown in the crystal growing incubator. The present specification states that for

> the hanging drop configuration, a crystallization drop of about 2ml forms a hanging drop of about 1-2 mm in diameter...the X-ray beam preferably has a focus size of 200 microns or less. Being that a potential crystal could be found at any position within this drop, the tightly focused X-ray beam must be precisely aligned to irradiate the potential crystal....Use of the imaging system reduces the exposure of a crystallization drop to X-rays, as the crystallization drop need not be exposed to an X-ray beam until a potential crystal has been located.[12]

As Tatsumi presupposes the presence of crystalline material, there is no motivation to combine the Tatsumi apparatus with an imaging system, such as the Fink imaging system. In other words, Tatsumi already assumes that crystalline material is present, and, therefore, does not need an imaging system to first locate the presence of a crystal. Accordingly, there is no suggestion or motivation to modify or combine the reference teachings of Tatsumi or Fink.

Moreover, Fink does not disclose an imaging system for the purpose of discovering and locating crystalline material in a drop (*in-situ* growth environment). In the present invention, the crystalline material in the crystallization solution is first identified and located, and is thereafter screened using X-ray diffraction.

In light of the above, it is respectfully requested that this rejection be withdrawn, and that claim 4 be allowed.

12. The Examiner has rejected claims 5-7 under 35 U.S.C. 103(a) as being unpatentable over Tatsumi as applied to claim 1, and further in view of Stettner. Applicants respectfully traverse this rejection.

The Examiner stated that Tatsumi "did not teach that the x-ray detector is a phosphor plate imaging system," and stated that it "would have been obvious to a person of ordinary skill in the art at the time the invention was made to employ a real-time phosphor plate imaging system for detecting diffracted x-rays, since a person would be motivated to obtain a result in real time." For at least the reasons stated above, Tatsumi does not teach detecting the

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[12] *See* page 12, line 22, to page 13, line 11.

presence of crystalline material as a method of improved screening of crystals and microcrystalline material with appropriate X-ray diffraction characteristics, as required by independent claim 1. In addition, Stettner also does not teach detecting the presence of crystalline material. Accordingly, the combination of Tatsumi and Stettner do not teach or suggest all the claim limitations of Independent claim 1, from which claims 5-6 depends. (Claim 7 has been canceled).

In light of the above, it is respectfully requested that this rejection be withdrawn, and that claims 5-6 be allowed.

13. The Examiner has rejected claim 8 under 35 U.S.C. 103(a) as being unpatentable over Tatsumi as applied to claim 1, and further in view of Cullity. Applicants respectfully traverse this rejection.

The Examiner stated that Tatsumi "did not teach that the x-ray source emits a monochromatic beam of x-rays consisting of CuKα radiation" and that "Cullity disclosed that CuKα radiation is generally the most useful among the characteristic radiations in x-ray diffraction." For at least the reasons stated above, Tatsumi does not teach detecting the presence of crystalline material as a method of improved screening of crystals and microcrystalline material with appropriate X-ray diffraction characteristics, as required by independent claim 1. In addition, Cullity also does not teach detecting the presence of crystalline material. Accordingly, the combination of Tatsumi and Cullity do not teach or suggest all the claim limitations of Independent claim 1, from which claim 8 depends.

In light of the above, it is respectfully requested that this rejection be withdrawn, and that claim 8 be allowed.

14. The Examiner has rejected claim 9 under 35 U.S.C. 103(a) as being unpatentable over Tatsumi as applied to claim 1, and further in view of Dosho. Applicants respectfully traverse this rejection.

The Examiner stated that "Tatsumi *et al.* did not teach that the x-ray source emits an x-ray beam with a focus size of 200 microns or less," and that "Dosho disclosed a micro-diffraction apparatus that is capable of producing a beam spot size of 100µ or less." For at least the reasons stated above, Tatsumi does not teach detecting the presence of crystalline

material as a method of improved screening of crystals and microcrystalline material with appropriate X-ray diffraction characteristics, as required by independent claim 1. In addition, Dosho also does not teach detecting the presence of crystalline material. Accordingly, the combination of Tatsumi and Dosho do not teach or suggest all the claim limitations of Independent claim 1, from which claim 9 depends.

In light of the above, it is respectfully requested that this rejection be withdrawn, and that claim 9 be allowed.

15. The Examiner has rejected claim 10 under 35 U.S.C. 103(a) as being unpatentable over Tatsumi as applied to claim 1, and further in view of Polichar. Applicants respectfully traverse this rejection.

The Examiner stated that Tatsumi "did not teach that the apparatus further comprising a transmitter that transmits information associated with the diffraction pattern to a remote location." And that Polichar "disclosed an x-ray system that comprises a transmitter (modem, Ethernet). For at least the reasons stated above, Tatsumi does not teach detecting the presence of crystalline material as a method of improved screening of crystals and microcrystalline material with appropriate X-ray diffraction characteristics, as required by independent claim 1. In addition, Polichar also does not teach detecting the presence of crystalline material. Accordingly, the combination of Tatsumi and Polichar do not teach or suggest all the claim limitations of Independent claim 1, from which claim 10 depends.

Moreover, Polichar teaches a X-ray apparatus that:

> . . .digitally acquires, processes, displays, stores, and/or transmits electronic radioscopic images of sealed packages, containers and other objects, including patients, on location for security, customs, medical, and other non-destructive and non-invasive purposes[13]. (Emphasis added).

However, claim 10 requires a "transmitter that transmits information associated with said diffraction pattern to a remote location"(Emphasis added). Accordingly, Polichar discloses transmitting X-ray images of packages or objects and not information associated with a diffraction pattern. Accordingly, neither Tatsumi nor Polichar disclose or teach transmitting diffraction patterns.

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[13]Polichar, col. 1, ll. 14-19.

Still further, neither of the references provide motivation to combine an apparatus that may be used to screen multiple crystal growing incubators to detect the presence of appropriately diffracting crystals with a transmitter to transmit diffraction patterns. This apparatus may be used on Earth, or, for example, in space. Thus, the inventors recognized a need for the use of a transmitter where an expert is not available to constantly monitor the progress of the screening experiment.

In light of the above, it is respectfully requested that this rejection be withdrawn, and that claim 10 be allowed.

16. The Examiner has rejected claims 17 and 18 under 35 U.S.C. 103(a) as being unpatentable over Tatsumi as applied to claim 16. Applicants respectfully traverse this rejection.

The Examiner stated that Tatsumi "did not teach storing the location of the crystalline material," and that it would have been "obvious to a person of ordinary skill in the art at the time the intention was made to store the location of the crystalline material, since a person would be motivated to automate the alignment procedure..." For at least the reasons stated above, Tatsumi does not teach detecting the presence of crystalline material as a method of improved screening of crystals and microcrystalline material with appropriate X-ray diffraction characteristics, as required by independent claim 11.

Moreover, neither Tatsumi, or knowledge generally available to one skilled in the art, provide motivation to combine the Tatsumi apparatus with a device to store the location of the crystalline material. Also, as stated above, the specification states that for

> . . .the hanging drop configuration, a crystallization drop of about 2ml forms a hanging drop of about 1-2 mm in diameter . . . the X-ray beam preferably has a focus size of 200 microns or less. Being that a potential crystal could be found at any position within this drop, the tightly focused X-ray beam must be precisely aligned to irradiate the potential crystal . . . Use of the imaging system reduces the exposure of a crystallization drop to X-rays, as the crystallization drop need not be exposed to an X-ray beam until a potential crystal has been located[14].

[14]*See* page 12, line 22, to page 13, line 11.

Also, according to the present invention, the same drop may be screened multiple times, once crystalline material is detected, storing the location of the crystalline material allows for time-saving on following screenings. Furthermore the present invention relates to screening crystal growth incubators for the presence of appropriately diffracting crystalline material that can be used for structure determination. The crystalline material may then be obtained from the incubator and placed in an X-ray diffraction device for structure determination. As Tatsumi presupposes the presence of crystalline material, Tatsumi does not teach a method of monitoring multiple crystal incubators for the presence of crystalline material, and Tatsumi does not teach a screening method for obtaining crystalline material that will then be used for structural analysis. Accordingly, there is no motivation to combine Tatsumi with knowledge generally available to one skilled in the art.

In light of the above, it is respectfully requested that this rejection be withdrawn, and that claim 17 and 18 be allowed.

17. The Examiner has rejected claim 21 under 35 U.S.C. 103(a) as being unpatentable over Tatsumi as applied to claim 20. Applicants respectfully traverse this rejection.

The Examiner stated that Tatsumi

> . . . did not teach growing the crystalline material by a method selected from the group consisting of: a vapor diffusion method, a hang-drop method, a sitting drop method, a dialysis method, a microbatch method, and a gel crystal growth method, . . . it would have been obvious to a person of ordinary skill in the art at the time the invention was made to perform this method in any growth environment . . . lack of criticality is demonstrated by applicant's claiming of a plurality of methods.

As stated above, Tatsumi does not teach detecting the presence of crystalline material as a method of improved screening of crystals and microcrystalline material with appropriate X-ray diffraction characteristics. Moreover, Tatsumi relates to methods of controlling crystal growth for use in semiconductors or optical devices,[15] and more specifically to a "method of monitoring a single crystal during growth...during growth of the crystal produced by a

[15] Tatsumi, col. 1, ll. 14-16.

pulling up method or a floating melting accumulation method."[16] In other words, Tatsumi teaches growing crystals for optical devices by a pulling up method or a floating melting accumulation method, and not a vapor diffusion method, a hanging-drop method, a sitting drop method, a dialysis method, a microbatch method, or a gel crystal growth method. In other words, Tatsumi teaches away from the present invention. Accordingly, there is no motivation or suggestion to combine Tatsumi with knowledge generally available to one skilled in the art. Indeed, rather than demonstrating a lack of criticality of methods, the screening methods named in claim 21 represent embodiments of the present invention that are especially improved using the methods of the present invention.

18. The Examiner has rejected claim 22 under 35 U.S.C. 103(a) as being unpatentable over Tatsumi as applied to claim 11, and further in view of Arnowitz. Applicants respectfully traverse this rejection.

The Examiner stated that Tatsumi "did not teach performing this method in space," and that Arnowitz "disclosed that space-grown crystals are of higher crystallographic perfection than earth-grown crystals." For at least the reasons stated above, Tatsumi does not teach detecting the presence of crystalline material as a method of improved screening of crystals and microcrystalline material with appropriate X-ray diffraction characteristics, as required by independent claim 11. In addition, Arnowitz also does not teach detecting the presence of crystalline material. Accordingly, the combination of Tatsumi and Arnowitz do not teach or suggest all the claim limitations of Independent claim 11, from which claim 22 depends.

In light of the above, it is respectfully requested that this rejection be withdrawn, and that claim 22 be allowed.

19. The Examiner has rejected claims 23 and 24 under 35 U.S.C. 103(a) as being unpatentable over Tatsumi as applied to claim 11. Applicants respectfully traverse this rejection.

The Examiner stated that Tatsumi "did not teach the method further comprising

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[16]Tatsumi, col. 1, ll. 6-11.

determining whether the crystalline material is a protein crystal or a salt crystal," and that "it would have been obvious to a person of ordinary skill in the art at the time the invention was made to determine whether the crystalline material is a protein crystal or a salt crystal, since a person in the art would be able to make that determination given the x-ray diffraction pattern." For at least the reasons stated above, Tatsumi does not teach <u>detecting the presence of crystalline material</u> as a method of improved screening of crystals and microcrystalline material with appropriate X-ray diffraction characteristics, as required by independent claim 11.

Moreover, Tatsumi relates to methods of controlling crystal growth for use in semiconductors or <u>optical devices</u>,[17] and more specifically to a "method of monitoring a single crystal during growth...during growth of the crystal <u>produced by a pulling up method or a floating melting accumulation method</u>."[18] Accordingly, Tatsumi provides no motivation for a method of screening for <u>protein crystal growth</u>, and thus no motivation for determining whether the crystalline material identified in the crystal incubator is a <u>protein or a salt</u>. Moreover, the Examiner has not pointed to a single reference that teaches, or provides motivation for, determining whether crystalline material identified in a crystallization drop is a salt or a protein.

In light of the above, it is respectfully requested that this rejection be withdrawn, and that claims 23-24 be allowed.

20. The Examiner has rejected claim 4 under 35 U.S.C. 103, as unpatentable over Murayama as applied to claim 1, and further in view of Fink. Applicants respectfully traverse this rejection.

The Examiner states that "Murayama et al. disclosed an apparatus and method for detecting the presence of crystalline material in its in situ growth environment comprising a crystal growth incubator. However, Murayama et al. did not teach that the apparatus further comprising an imaging system disposed adjacent to the crystal incubator," and cites Fink as disclosing a micro-diffractometer for aligning the x-ray with a micro-sized sample.

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[17]Tatsumi, col. 1, ll. 14-16.

[18]Tatsumi, col. 1, ll. 6-11.

Murayama does not teach the methods of the present invention, as Murayama presupposes the existence of crystalline material, and the present invention relates to detecting whether there is crystalline material at all, and, if the crystalline material detected has the appropriate diffraction characteristics. Accordingly, Murayama does not disclose the present invention.

Claim 4 relates to the addition of an imaging system as part of the crystalline detection apparatus to detect the presence and location of crystals grown in the crystal growing incubator. The present specification states that for

> the hanging drop configuration, a crystallization drop of about 2ml forms a hanging drop of about 1-2 mm in diameter...the X-ray beam preferably has a focus size of 200 microns or less. Being that a potential crystal could be found at any position within this drop, the tightly focused X-ray beam must be precisely aligned to irradiate the potential crystal....Use of the imaging system reduces the exposure of a crystallization drop to X-rays, as the crystallization drop need not be exposed to an X-ray beam until a potential crystal has been located.[19]

As Murayama presupposes the presence of crystalline material, there is no motivation in Murayama to combine the Murayama apparatus with an imaging system, such as the Fink imaging system. In other words, as crystals are presupposed, it is counter intuitive to first determine whether crystals are present.

Moreover, Fink does not disclose an imaging system for the purpose of discovering and locating crystalline material in a drop (*in-situ*). In the present invention, the crystalline material in the crystallization solution is first identified and located, and is then screened using X-ray diffraction.

In light of the above, it is respectfully requested that this rejection be withdrawn, and that claim 4 be allowed.

21. The Examiner has rejected claims 5-7 under 35 U.S.C. 103(a) as being unpatentable over Murayama as applied to claim 1, and further in view of Stettner. Applicants respectfully traverse this rejection.

The Examiner stated that Tatsumi [Applicant presumes that the Examiner meant Murayama] "did not teach that the x-ray detector is a phosphor plate imaging system," and

[19] *See* page 12, line 22, to page 13, line 11.

stated that it "would have been obvious to a person of ordinary skill in the art at the time the invention was made to employ a real-time phosphor plate imaging system for detecting diffracted x-rays, since a person would be motivated to obtain a result in real time." As stated above, Murayama does not teach detecting whether there is crystalline material at all, and, if the crystalline material detected has the appropriate diffraction characteristics. For at least this reason, it is respectfully requested that this rejection be withdrawn, and that claims 5-7 be allowed.

22. The Examiner has rejected claim 8 under 35 U.S.C. 103(a) as being unpatentable over Murayama as applied to claim 1, and further in view of Cullity. Applicants respectfully traverse this rejection.

The Examiner stated that Murayama "did not teach that the x-ray source emits a monochromatic beam of x-rays consisting of CuKa radiation" and that "Cullity disclosed that CuKa radiation is generally the most useful among the characteristic radiations in x-ray diffraction." As stated above, Murayama does not teach the methods of the present invention, as Murayama presupposes the existence of crystalline material, and the present invention relates to initially detecting whether crystalline material is present, and, if the crystalline material detected has the appropriate diffraction characteristics. Accordingly, the combination of the references do not teach all the limitations of the claim. For at least this reason, it is respectfully requested that this rejection be withdrawn, and that claim 8 be allowed.

23. The Examiner has rejected claim 9 under 35 U.S.C. 103(a) as being unpatentable over Murayama as applied to claim 1, and further in view of Dosho. Applicants respectfully traverse this rejection. The Examiner stated that "Murayama et al. did not teach that the x-ray source emits an x-ray beam with a focus size of 200 microns or less," and that "Dosho disclosed a micro-diffraction apparatus that is capable of producing a beam spot size of 100m or less." As stated above, Murayama does not teach the methods of the present invention, as Murayama presupposes the existence of crystalline material, and the present invention relates to initially detecting whether crystalline material is present, and, if the crystalline material detected has the appropriate diffraction characteristics. Accordingly, the combination of the

references do not teach all the limitations of the claim. For at least this reason, it is respectfully requested that this rejection be withdrawn, and that claim 9 be allowed.

24. The Examiner has rejected claim 10 under 35 U.S.C. 103(a) as being unpatentable over Murayama as applied to claim 1, and further in view of Polichar. Applicants respectfully traverse this rejection.

The Examiner stated that Murayama "did not teach that the apparatus further comprising a transmitter that transmits information associated with the diffraction pattern to a remote location" and that Polichar "disclosed an x-ray system that comprises a transmitter (modem, Ethernet). As stated above, Murayama does not teach the methods of the present invention as Murayama presupposes the existence of crystalline material, and the present invention relates to detecting whether there is crystalline material at all, and, if the crystalline material detected has the appropriate diffraction characteristics.

In addition, Polichar also does not teach detecting the presence of crystalline material. Accordingly, the combination of Tatsumi and Polichar do not teach or suggest all the claim limitations of Independent claim 1, from which claim 10 depends.

Moreover, Polichar teaches a X-ray apparatus that:

> . . .digitally acquires, processes, displays, stores, and/or transmits electronic radioscopic images of sealed packages, containers and other objects, including patients, on location for security, customs, medical, and other non-destructive and non-invasive purposes[20]. (Emphasis added).

However, claim 10 requires a "transmitter that transmits information associated with said diffraction pattern to a remote location"(Emphasis added). Accordingly, Polichar discloses transmitting X-ray images of packages or objects and not information associated with a diffraction pattern. Accordingly, neither Tatsumi nor Polichar disclose or teach transmitting diffraction patterns.

Moreover, neither of these references provide any suggestion to motivation to combine the Murayama apparatus with a transmitter. The present invention provides an apparatus that may be used to screen multiple crystal growing incubators to detect the presence of appropriately diffracting crystals. This apparatus may be used on Earth, or, for

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[20]Polichar, col. 1, ll. 14-19.

example, in space. Thus, the inventors recognized a need for the use of a transmitter where an expert is not available to constantly monitor the progress of the screening experiment. In contrast, Murayama is directed to monitoring the growth of a single crystal;[21] Accordingly no motivation is provided to combine the Murayama reference with a transmitter so that an expert at a remote location may review data.

In light of the above, it is respectfully requested that this rejection be withdrawn, and that claim 10 be allowed.

25. The Examiner has rejected claims 17 and 18 under 35 U.S.C. 103(a) as being unpatentable over Murayama as applied to claim 16. Applicants respectfully traverse this rejection. The Examiner stated that Murayama "did not teach storing the location of the crystalline material," and that it would have been "obvious to a person of ordinary skill in the art at the time the invention was made to store the location of the crystalline material, since a person would be motivated to automate the alignment procedure..." As stated above, Murayama does not teach the methods of the present invention as Murayama presupposes the existence of crystalline material, and the present invention relates to detecting whether there is crystalline material at all, and, if the crystalline material detected has the appropriate diffraction characteristics.

Moreover, neither of these references provide any suggestion to motivation to combine the Murayama apparatus with a device to store the location of the crystalline material. Also, as stated above, the specification states that for

> the hanging drop configuration, a crystallization drop of about 2ml forms a hanging drop of about 1-2 mm in diameter...the X-ray beam preferably has a focus size of 200 microns or less. Being that a potential crystal could be found at any position within this drop, the tightly focused X-ray beam must be precisely aligned to irradiate the potential crystal....Use of the imaging system reduces the exposure of a crystallization drop to X-rays, as the crystallization drop need not be exposed to an X-ray beam until a potential crystal has been located[22].

Also, following the present invention, the same drop may be screened multiple times,

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[21]Murayama, col. 1, ll. 7-10.

[22]*See* page 12, line 22, to page 13, line 11.

once crystalline material is detected, storing the location of the crystalline material allows for time-saving on following screenings. Furthermore the present invention relates to screening crystal growth incubators for the presence of appropriately diffracting crystalline material that can be used for structure determination. The crystalline material may then be obtained from the incubator and placed in an X-ray diffraction device for structure determination. As Murayama presupposes the presence of crystalline material, Murayama does not teach a method of monitoring multiple crystal incubatiors for the presence of crystalline material, and Murayama does not teach a screening method for obtaining crystalline material that will then be used for structural analysis. Accordingly, there is no motivation in Murayama to combine the Murayama apparatus with a device for storing the location of the crystal.

In light of the above, it is respectfully requested that this rejection be withdrawn, and that claims 17 and 18 be allowed.

26. The Examiner has rejected claim 21 under 35 U.S.C. 103(a) as being unpatentable over Murayama as applied to claim 20. Applicants respectfully traverse this rejection.

The Examiner stated that Murayama "did not teach growing the crystalline material by a method selected from the group consisting of: a vapor diffusion method, a hang-drop method, a sitting drop method, a dialysis method, a microbatch method, and a gel crystal growth method," and that "it would have been obvious to a person of ordinary skill in the art at the time the invention was made to perform this method in any growth environment..." and that the "lack of criticality is demonstrated by applicant's claiming of a plurality of methods." Applicants respectfully disagree with the Examiner's contention. As stated above, Murayama does not teach the methods of the present invention as Murayama presupposes the existence of crystalline material, and the present invention relates to detecting whether there is crystalline material at all, and, if the crystalline material detected has the appropriate diffraction characteristics.

Moreover, Murayama relates to a method of measuring the lattice constant ratio of a crystal during heating in a heating furnace[23]. Murayama provides no motivation, therefore, to use a method of screening for crystal growth such as those named in claim 21. Rather than

[23]Murayama, col. 2, ll. 51-54.

demonstrating a lack of criticality of methods, those screening methods named in claim 21 represent embodiments of the present invention that are especially improved using the methods of the present invention.

In light of the above, it is respectfully requested that this rejection be withdrawn, and that claim 21 be allowed.

27. The Examiner has rejected claim 22 under 35 U.S.C. 103(a) as being unpatentable over Murayama as applied to claim 11, and further in view of Arnowitz. Applicants respectfully traverse this rejection.

The Examiner stated that Murayama "did not teach performing this method in space," and that Arnowitz "disclosed that speace-grown crystals are of higher crystallographic perfection than earth-grown crystals." As stated above, Murayama does not teach the methods of the present invention as <u>Murayama presupposes the existence of crystalline material</u>, and the present invention relates to <u>detecting whether there is crystalline material at all</u>, and, if the crystalline material detected has the appropriate diffraction characteristics.

In light of the above, it is respectfully requested that this rejection be withdrawn, and that claim 22 be allowed.

28. The Examiner has rejected claim 23 and 24 under 35 U.S.C. 103(a) as being unpatentable over Murayama et al. as applied to claim 11. Applicants respectfully traverse this rejection. The Examiner stated that Murayama "did not teach the method further comprising determining whether the crystalline material is a protein crystal or a salt crystal," and that "it would have been obvious to a person of ordinary skill in the art at the time the invention was made to determine whether the crystalline material is a protein crystal or a salt crystal, since a person in the art would be able to make that determination given the x-ray diffraction pattern."As stated above, Murayama does not teach the methods of the present invention as <u>Murayama presupposes the existence of crystalline material</u>, and the present invention relates to <u>detecting whether there is crystalline material at all</u>, and, if the crystalline material detected has the appropriate diffraction characteristics.

Moreover, Murayama relates to a method of measuring the lattice constant ratio of a

crystal during heating in a heating furnace[24]. Therefore, no motivation is provided for a method of screening for protein crystal growth, and thus no motivation for determining whether the crystalline material detected in the crystal incubator is a protein or a salt. Moreover, the Examiner has not pointed to a single reference that teaches, or provides motivation for, determining whether crystalline material identified in a crystallization drop is salt or protein.

In light of the above, it is respectfully requested that this rejection be withdrawn, and that claims 23 and 24 be allowed.

29. The Examiner has rejected claim 25-27 under 35 U.S.C. 103(a) as being unpatentable over Murayama. Applicants respectfully traverse this rejection.

The Examiner stated that "Murayama did not teach that the method comprises the steps of storing the location of the crystal," but that "it would have been obvious to a person of ordinary skill in the art at the time the invention was made to store the location of the crystal." As stated above, Murayama does not teach the methods of the present invention as <u>Murayama presupposes the existence of crystalline material</u>, and the present invention relates to <u>detecting whether there is crystalline material at all</u>, and, if the crystalline material detected has the appropriate diffraction characteristics.

Moreover, no motivation is provided for combining the Murayama apparatus with a device to store the location of the crystalline material. Also, as stated above, the specification states that for

> the hanging drop configuration, a crystallization drop of about 2ml forms a hanging drop of about 1-2 mm in diameter...the X-ray beam preferably has a focus size of 200 microns or less. Being that a potential crystal could be found at any position within this drop, the tightly focused X-ray beam must be precisely aligned to irradiate the potential crystal....Use of the imaging system reduces the exposure of a crystallization drop to X-rays, as the crystallization drop need not be exposed to an X-ray beam until a potential crystal has been located[25].

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[24]Murayama, col. 2, ll. 51-54.

[25]*See* page 12, line 22, to page 13, line 11.

Also, following the present invention, the same drop may be screening multiple times, once crystalline material is detected, storing the location of the crystalline material allows for time-saving on following screenings. Furthermore the present invention relates to screening crystal growth incubators for the presence of appropriately diffracting crystalline material that can be used for structure determination. The crystalline material may then be obtained from the incubator and placed in an X-ray diffraction device for structure determination. As Murayama presupposes the presence of crystalline material, Murayama does not teach a method of monitoring multiple crystal incubatiors for the presence of crystalline material, and Murayama does not teach a screening method for obtaining crystalline material that will then be used for structural analysis, there is no motivation in Murayama to combine the Murayama apparatus with a device for storing the location of the crystal.

In light of the above, it is respectfully requested that this rejection be withdrawn, and that claims 25-27 be allowed.

30. The Examiner has rejected claim 28 under 35 U.S.C. 103(a) as being unpatentable over Murayama as applied to claim 25, and in view of Fink. Applicants respectfully traverse this rejection.

The Examiner stated that "Murayama did not teach re-positioning the crystalline material relative to the x-ray beam while the x-ray beam remains stationary;" and that Fink "disclosed an x-ray micro-diffractometer comprising an XYZ sample stage." As stated above, Murayama does not teach the methods of the present invention as <u>Murayama presupposes the existence of crystalline material</u>, and the present invention relates to <u>detecting whether there is crystalline material at all</u>, and, if the crystalline material detected has the appropriate diffraction characteristics.

In addition, claim 28 relates to the addition of positioning system to align the X-ray beam with the crystalline material. Also, as stated above, the specification states that for

> the hanging drop configuration, a crystallization drop of about 2ml forms a hanging drop of about 1-2 mm in diameter...the X-ray beam preferably has a focus size of 200 microns or less. Being that a potential crystal could be found at any position within this drop, the tightly focused X-ray beam must be precisely aligned to irradiate the potential crystal....Use of the imaging system reduces the exposure of a crystallization drop to X-rays, as the crystallization drop need not be exposed to an X-ray beam until a potential crystal has been

located[26].

As Murayama presupposes the presence of crystalline material, there is no motivation in Murayama to combine the Murayama apparatus with an positioning system, such as the Fink XYZ sample stage.

In light of the above, it is respectfully requested that this rejection be withdrawn, and that claim 28 be allowed.

31. The Examiner has rejected claim 29 under 35 U.S.C. 103(a) as being unpatentable over Murayama as applied to claim 25, and in view of Arnowitz. Applicants respectfully traverse this rejection.

The Examiner stated that "Murayama did not teach performing this method in space," and that Arnowitz "disclosed that space-grown crystals are of higher crystallographic perfection than earth-grown crystals." As stated above, Murayama does not teach the methods of the present invention as Murayama presupposes the existence of crystalline material, and the present invention relates to detecting whether there is crystalline material at all, and, if the crystalline material detected has the appropriate diffraction characteristics.

In light of the above, it is respectfully requested that this rejection be withdrawn, and that claim 29 be allowed.

32. The Examiner has rejected claims 30 and 31 under 35 U.S.C. 103(a) as being unpatentable over Murayama as applied to claim 25. Applicants respectfully traverse this rejection.

The Examiner stated that "Murayama did not teach determining whether the crystalline material is a protein crystal or a salt crystal," and that "it would have been obvious to a person of ordinary skill in the art at the time the invention was made to determine whether the crystalline material is a protein crystal or a salt crystal, since a person in the art would be able to make that determination given the x-ray diffraction pattern." As stated above, Murayama does not teach the methods of the present invention as Murayama presupposes the existence of crystalline material, and the present invention relates to

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[26]*See* page 12, line 22, to page 13, line 11.

detecting whether there is crystalline material at all, and, if the crystalline material detected has the appropriate diffraction characteristics.

Moreover, Murayama relates to a method of measuring the lattice constant ration of a crystal during heating in a heating furnace[27]. Therefore, no motivation is provided for a method of screening for protein crystal growth, and thus no motivation for determining whether the crystalline material detected in the crystal incubator is a protein or a salt.

In light of the above, it is respectfully requested that this rejection be withdrawn, and that claims 30 and 31 be allowed.

CONCLUSION

In view of the foregoing, it is respectfully submitted that the application is now in a condition for allowance. Should the Examiner believe that a telephone interview would help advance the prosecution of this case, the Examiner is requested to contact the undersigned attorney at 650-849-7603.

If there are any fees or credits due in connection with the filing of this Amendment, including any fees required for an Extension of Time under 37 C.F.R. Section 1.136, authorization is given to charge any necessary fees to our Deposit Account No. 16-1150 (order no. 10342-0010-999). A copy of this sheet is enclosed for such purpose.

Respectfully submitted,

Date February 20, 2003 45,645

Dion M. Bregman (Reg. No.)
For: Laura A. Coruzzi (Reg. No. 30,742)

PENNIE & EDMONDS LLP
3300 Hillview Avenue
Palo Alto, CA 94304
(650) 493-4935

[27]Murayama, col. 2, ll. 51-54.

COPY

detecting whether there is crystalline material at all, and, if the crystalline material detected has the appropriate diffraction characteristics.

Moreover, Murayama relates to a method of measuring the lattice constant ration of a crystal during heating in a heating furnace[27]. Therefore, no motivation is provided for a method of screening for protein crystal growth, and thus no motivation for determining whether the crystalline material detected in the crystal incubator is a protein or a salt.

In light of the above, it is respectfully requested that this rejection be withdrawn, and that claims 30 and 31 be allowed.

CONCLUSION

In view of the foregoing, it is respectfully submitted that the application is now in a condition for allowance. Should the Examiner believe that a telephone interview would help advance the prosecution of this case, the Examiner is requested to contact the undersigned attorney at 650-849-7603.

If there are any fees or credits due in connection with the filing of this Amendment, including any fees required for an Extension of Time under 37 C.F.R. Section 1.136, authorization is given to charge any necessary fees to our Deposit Account No. 16-1150 (order no. 10342-0010-999). A copy of this sheet is enclosed for such purpose.

Respectfully submitted,

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[27]Murayama, col. 2, ll. 51-54.

APPENDIX A

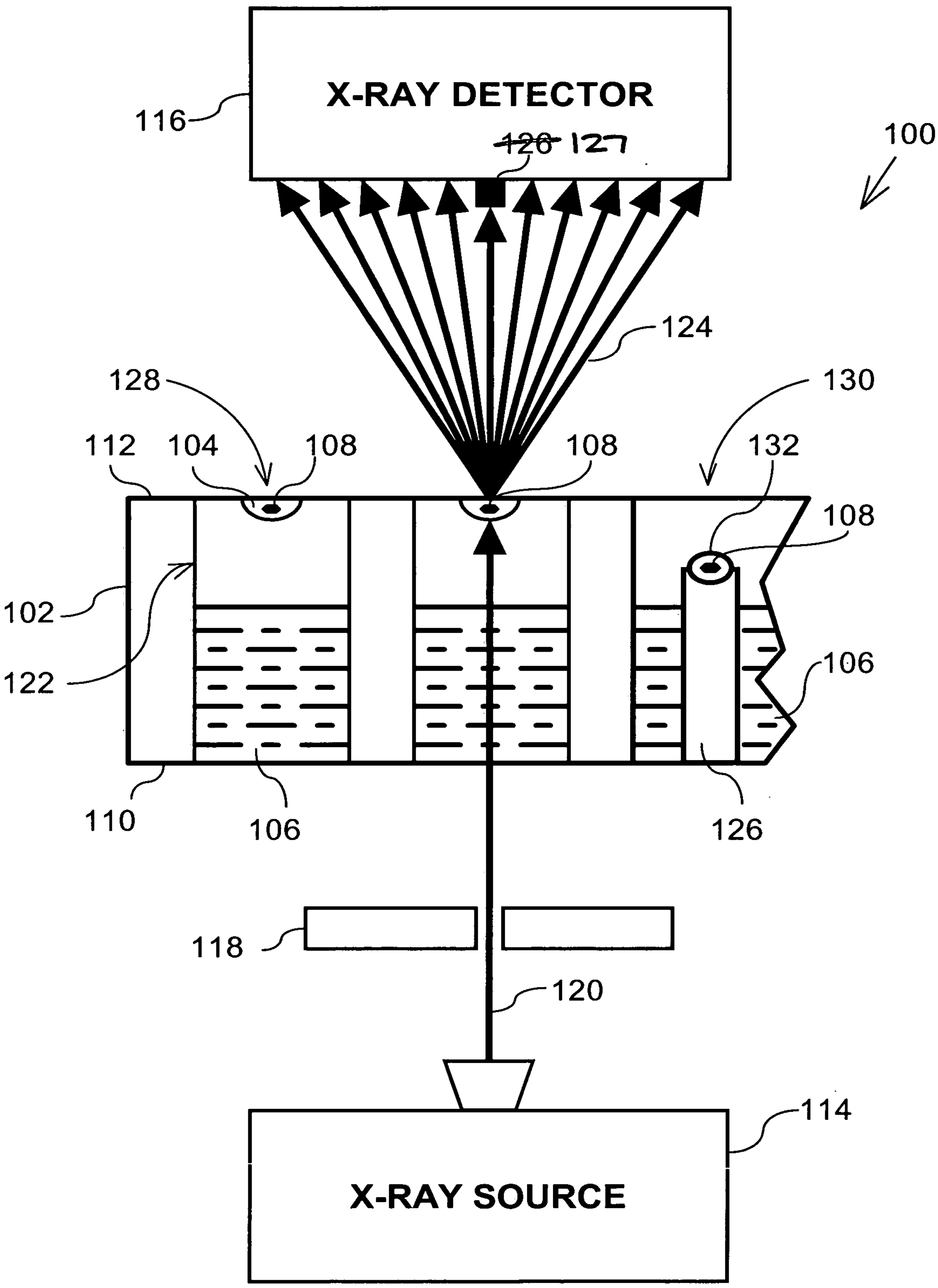
X-RAY DETECTOR
116
~~126~~ 127
100
124
128
130
112
104
108
108
132
108
102
122
106
110
106
126
118
120
114
X-RAY SOURCE

FIG. 1

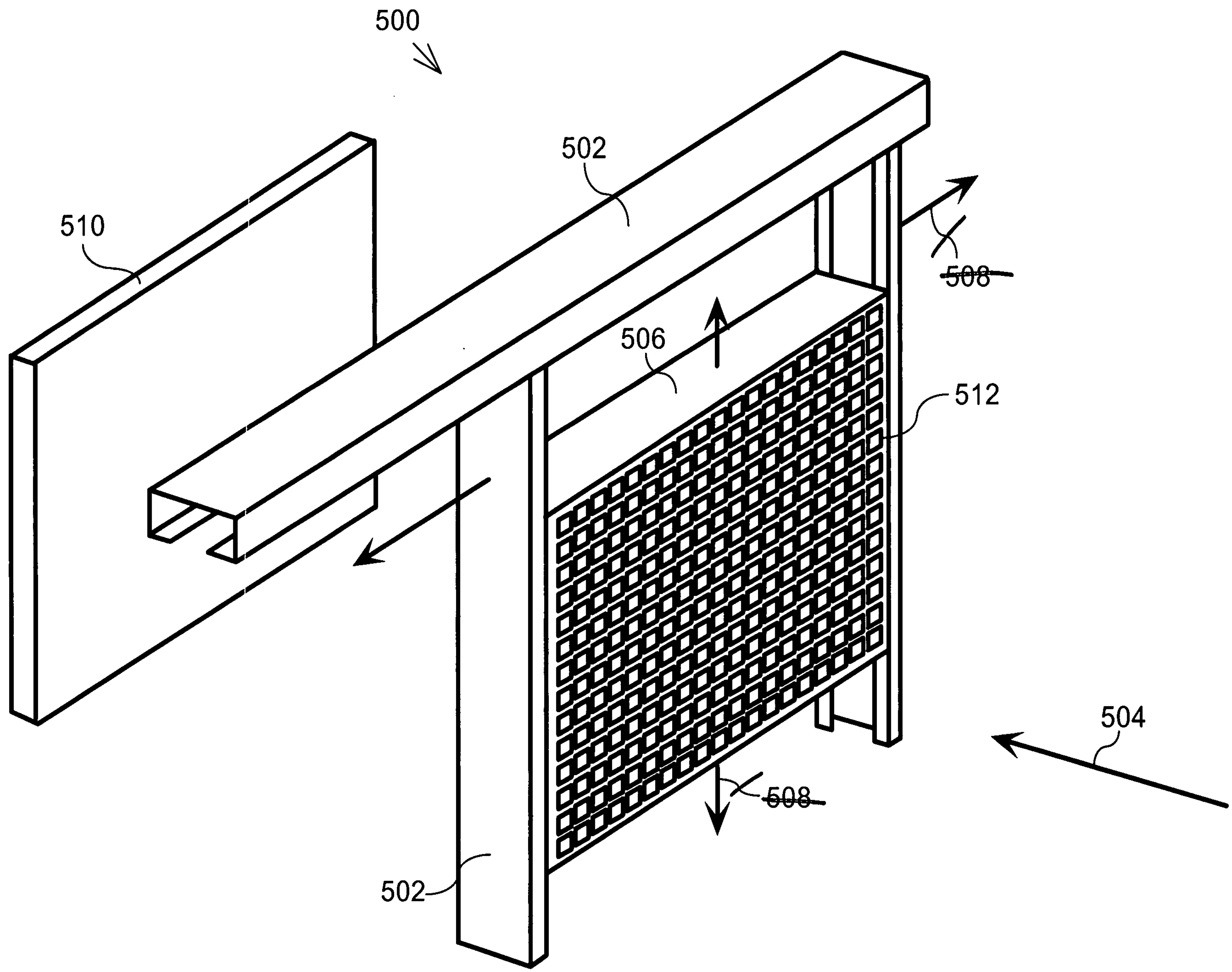

FIG. 5

APPENDIX C

APPENDIX C
Marked-up Version of the Specification

Please replace the second paragraph on page 9 with the following paragraph:

In the sitting drop configuration **130**, a drop **132** of crystallization solution is placed in a receptacle on the top of an upstanding column **126** where conditions lead to supersaturation in the drop [128] 132 and the initiation of precipitation which forms a crystal **108**.

Please replace the second paragraph on page 12 with the following paragraph:

In a preferred embodiment, a beam-stop [126] 127 is provided between the incubator **102** and the X-ray detector **116** to stop a central non-diffracted X-ray beam from damaging the detector or adversely affecting the results. The spot size of the X-ray beam **120** at the detector (or beam stop) is preferably about 40 to 50 microns in diameter, with a divergence of no greater than 30 arc-seconds. A means for inserting a calibration crystal into the X-ray beam, is also preferably provided to calibrate the apparatus **100**.

Please replace the paragraph starting on page 14, line 16 and ending on page 15, line 8 with the following paragraph:

Figure 4 _ is a flow chart of a method of screening for crystals according to an embodiment of the invention. The incubator **102 (Figure 1)** is preferably first placed (step **402**) onto the positioner **300 (Figure 3)**. The incubator **102** can conveniently be placed with a "pick and place" robot arm known to those of skill in the art. The imaging system **202 (Figure 2)** is then preferably activated (step **404**) and moved over the incubator. Alternatively, the positioner can move the incubator relative to the imaging system. The activation (step **404**) of the imaging system entails scanning each well **122** to determine (step **418**) the presence and/or location (step **416**) of a potential crystal. The imaging system **202**, therefore, scans each well of the incubator for potential crystal material such as single crystals and microcrystals. The location of each visually acceptable potential crystal is then preferably stored

(step **406**) by the imaging system. The imaging system is then retracted from its scanning position adjacent to the incubator. Using the stored location of each potential crystal, the positioner moves the incubator **102** or the X-ray detector **116** to align or position (step **408**) each potential crystal with a line coincident with the emitted X-ray beam. Each located potential crystal is then irradiated (step **410**) by the X-ray beam **120 (Figure 1)** emitted from the X-ray source **114 (Figure 1)**. The X-ray detector **116 (Figure 1)** detects (step **412**) any diffraction from the irradiated crystal, whereafter the detected diffraction patterns are stored and/or analyzed. The positioner can optionally locate the next potential crystal (step **414**) and the process can be optionally repeated until all detected crystals have been irradiated and their diffraction patterns stored and/or analyzed, where the diffraction patten indicates the presence of one or more well ordered crystal. The overall time to assess the quality of diffraction of a single crystal is approximately 5 minutes.

Please replace the final paragraph on page 16 with the following paragraph:

All exposures led to a diffraction pattern that had a band of diffuse scattering **602 (Figure 6)** which was centered around 4 - 5 Å resolution. This 4 - 5 Å band was probably due to diffraction from paraffin oil. On several, but not all, exposures, a second scattering ring centered around 8Å appeared. Since this second band appeared at exposures corresponding to approximately 2.5 mm translations of the plate, this ring was probably due to scattering from the walls of the wells of the plate which are spaced 2.25 mm apart. Some samples yielded no X-ray diffraction indicating that the X-ray beam did not pass through crystalline material. However, when the X-ray beam passed through some of the samples of lysozyme, intense diffraction patterns were observed indicating the presence of well-ordered crystals in the samples. Further exposures showed that one could observe diffraction out to 1.8Å from the lysozyme crystal *in-situ*. Examples of diffraction of the crystal are referenced by numeral **606**. It can also be observed that no diffraction occurs

at the center **604** of the image due to placement of the beam stop **[126]** **<u>127</u>** **(Figure 1)**.

APPENDIX D

APPENDIX D
Marked-up Version of the Claims

Please cancel claim 7.

Please amend claims 1, 11, and 25 as follows:

1. (Amended) An apparatus for detecting the presence of <u>suitable</u> crystalline material in its in-situ growth environment, comprising:

a crystal growing incubator having opposing first and second sides;

an X-ray system, comprising:

an X-ray source disposed adjacent to said first side of said crystal growing incubator, where said X-ray source is configured to irradiate crystalline material grown in said crystal growing incubator; and

an X-ray detector disposed adjacent to said second side of said crystal growing incubator, where said X-ray detector is configured to detect the presence of diffracted X-rays from crystalline material grown in said crystal growing incubator; and

such that in use, crystalline material grown in said incubator can be <u>identified and</u> screened for suitability by said X-ray system, thereby, facilitating the increased reproducibility of successful crystal growth experiments.

11. (Amended) A method of screening for <u>suitable</u> crystalline material in its in-situ growth environment, said method comprising the steps of:

<u>identifying crystalline material in its in-situ growth environment;</u>

irradiating crystalline material in [its] <u>said</u> in-situ growth environment with an X-ray beam;

detecting a diffraction pattern from said crystalline material; and

screening said crystalline material for suitability based on said diffraction pattern.

25. (Amended) A method of screening for <u>suitable</u> crystalline material in its in-situ growth environment, said method comprising the steps of:

growing crystalline material in a crystal growing incubator;

placing said crystal growing incubator into a positioner;

determining the presence of said crystalline material in said crystal growing incubator;

ascertaining the location of said crystalline material in said crystal growing incubator;

storing the location of said crystalline material;

positioning said crystal growing incubator and an X-ray source relative to each another based on the location of said crystalline material, such that an X-ray beam emitted from said X-ray source accurately aligns with said crystalline material;

irradiating said crystalline material with said X-ray beam;

detecting with a X-ray detector, a diffraction pattern from said crystalline material; and

screening said crystalline material for suitability based on said diffraction pattern.

Please add the following two claims:

32. (New) The apparatus of claim 1, wherein said X-ray detector comprises a CCD camera comprising a phosphor screen.

33. (New) The apparatus of claim 32, wherein said phosphor screen achieves at least 4 to 8 line-pairs per millimeter resolution.

34. (New) An apparatus for detecting the presence of crystalline material in its in-situ growth environment, comprising:

a crystal growing incubator having opposing first and second sides, where the crystal growing incubator includes an array of crystal growth environments;

an X-ray system, comprising:

an X-ray source disposed adjacent to said first side of said crystal growing incubator, where said X-ray source is configured to irradiate crystalline material grown in said crystal growing incubator; and

an X-ray detector disposed adjacent to said second side of said crystal growing incubator, where said X-ray detector is configured to detect the

presence of diffracted X-rays from crystalline material grown in said crystal growing incubator;

a positioner configured to sequentially align each of said crystal growth environments and said X-ray system with one another; and

such that in use, crystalline material grown in said incubator can be screened for suitability by said X-ray system, thereby, facilitating the increased reproducibility of successful crystal growth experiments.

35. (New) The apparatus of claim 34, further comprising an imaging system disposed adjacent to said crystal growing incubator, where said imaging system detects the presence and location of crystals grown in said incubator, such that in use an X-ray beam emanating from said X-ray source is accurately aligned with crystals detected by said imaging system.

36. The apparatus of claim 34, wherein said X-ray detector is selected from a group consisting of: a charged coupled device (CCD) camera and an imaging plate system.

37. (New) The apparatus of claim 34, wherein said X-ray detector comprises a CCD camera comprising a phosphor screen.

38. (New) The apparatus of claim 37, wherein said phosphor screen achieves at least 4 to 8 line-pairs per millimeter resolution.